REMARKS

I. Status of the Claims

Claims 1, 3-6 and 8-13 are pending in the application, and claims 1, 6, 8, 9 and 11-13 stand withdrawn pursuant to a restriction requirement. Claims 3-5 and 10 stand rejected, variously, under 35 U.S.C. §102 and 35 U.S.C. §103. The specific grounds for rejection, and applicants' response thereto, are set out in detail below.

II. Incorporation by Reference / Amendment of the Specification

A. Correction of "Incorporation" Language under 37 C.F.R. §1.57(g)(1)

MPEP §608.01(p) sets forth the procedure for correcting an incorrect incorporation of a prior reference that fails to satisfy the specific language requirement of 37 C.F.R. §1.57(b)(1). As stated in 37 C.F.R. §1.57(g)(1), a correction to comply with paragraph (b)(1) is permitted if the application as filed clearly conveys an intent to incorporate the material by reference, whereas a "mere reference to material" does not convey an intent to incorporate the material by reference.

The relevant language from the instant application is as follows:

> The term Annexin V is well know to those skilled in the art and is used, for example, in documents cited above, for example, EP 1 379 266. As will be apparent to the skilled person, the N-terminal fragment of Annexin V is large enough to be recognisable by the skilled person as a fragment of Annexin V (rather than, for example, a fragment of another annexin[])].
>
> The pharmaceutical composition may comprise an effective amount of the Annexin V protein or N-terminal fragment of Annexin V, optionally in combination with a carrier and additives. Suitable carriers and additives which can be used will be well known to those skilled in the art, including the examples used in EP 1 379 266 ....

Specification at page 5, lines 10-20. Considering that Annexin V was an element of the original claims, this attempt to define that claim element by reference to a prior EP patent leaves little question regarding the importance of the citation, and further, that the applicant clearly intended to incorporate the relevant information from the reference, and not merely mention it in passing. As such, it is respectfully submitted that the proposed "incorporation by reference" language may be properly added to the specification.

B. Amendment of the Specification under 37 C.F.R. §1.57(f)

MPEP §608.01(p) also addresses, by reference to 37 C.F.R. §1.57(f), corrections of incorporation by reference by inserting the essential material previously incorporated by reference. A non-compliant incorporation by reference statement may be corrected by an amendment, but the amendment must not include new matter. For example, an incorporation by reference of essential material to an unpublished U.S. patent application, a foreign application or patent, or to a publication is improper under 37 CFR §1.57(c), and is not effective to incorporate the material ***unless corrected by the applicant under 37 C.F.R. §1.57(g)***. Further, a statement that the material being inserted is the material previously incorporated by reference, and that the amendment contains no new matter, is also required. See 37 CFR §1.57(f); see also *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). Applicants hereby make that statement.

Provided above is an amendment that introduces the salient portions of EP 1 379 266, which is improperly incorporated by reference by virtue of the concurrent amendment under 37 C.F.R. §1.57(g)(1). The incorporated sections provide definition for Annexin V, as indicated in

the paragraphs at page 5, lines 10-21, of the application as filed. Given compliance with 37 C.F.R. §1.57(f), applicants submit that introduction of the amendatory material, which does not constitute new matter, is proper.

For reference, applicants direct the examiner to the published counterpart of EP 1 379 266, PCT/US02/05079. The relevant passages, inserted by amendment into the present specification, can be found at page 7, line 26, to page 8, line 1, page 11, lines 23-27, and page 34, line 24 to page 35, line 30.

III. Rejection Under 35 U.S.C. §102

Claims 4 and 10 remain rejected as anticipated by Blankenberg *et al.*. The examiner maintains that even though the reference discloses the use of Annexin V merely as a targeting component of a larger composition, the present claims fail to distinguish that subject matter. Applicants traverse, but in the interest of advancing the prosecution, the claims have been further amended to recite that the Annexin V is native Annexin V, or a dimer and/or PEG conjugate of the native Annexin V or salt thereof. Support for the amendment is found in the specification as follows:

> The term "native" is literally supported by the Abstract.
>
> The term "native" is generally derivable from the application, which states that modification of Annexin V (for example, by PEGylation, dimerisation, or the formation of a salt) is only optional, and therefore unmodified, that is "native" Annexin V, is clearly taught to be of use in the present invention.
>
> The term "dimer" is supported by the disclosures of dimers of Annexin V incorporated from EP 1 379 266, in particular the passage incorporated from page 11 lines 26-27 of EP 1 379 266 which states that "One such modified annexin is a dimer of annexin V".
>
> The term "PEG conjugate" is supported by the disclosures of PEG conjugates of Annexin V incorporated from EP 1 379 266.

Further support for the PEG conjugate of Annexin V can found at page 2, lines 9-22 of the current application as originally filed, which teaches that PEGylation can increase half-life of Annexin V and, although this is said to be not necessary in the practice of the present invention, a "composition for injection comprising Annexin V or an N-terminal fragment of Annexin V ***with or without additives*** will thus prevent atherothrombosis by stabilizing the carotid plaque through an instant binding" (emphasis added). In this context, when the disclosure from page 2, lines 9-22 is read as a whole, it will be apparent that reference to "additives" is clearly a reference to PEGylation. Thus, it is also disclosed in the originally-filed application, even without the need to incorporate material from EP 1 379 266, that the invention can be practiced with PEGylated Annexin V.

The significance of the language introduced by the amendment provided above is discussed below. Referring to the Abstract of Blankenberg *et al.*:

> The present invention relies on the affinity of stressed or apoptotic cells for exogenously administered annexin V to create a multi-functional molecular probe that can be simultaneously used for imaging (localization of unstable plaque within the body) and therapy (treatment of unstable plaque).

The abstract specifically refers to the use of a "multi-functional molecular probe" that is created using annexin V, ***but not Annexin V itself***, for treatment of unstable plaques. In this complex, Annexin V is included as a binding component. Also necessarily included in the complex of Blankenberg *et al.* are a cytotoxic moiety (the "effector portion") and a localization moiety (the "targeting portion"), where the effector portion is said to kill or inhibit stressed or apoptotic cells associated with vulnerable plaques. Thus, to the extent that Blankenberg *et al.* describes any use for Annexin V in respect of the treatment of vulnerable plaques, this suggestion is limited only to the context of Annexin V being used as a "binding component," and further only in the context

of the Annexin V molecule being presented in a form that is complexed to additional "effector" and "targeting" portions, such as technetium-99m and porphyrin, respectively.

The examiner remarks, in respect of Blankenberg's disclosure, that:

> ... under the broadest reasonable interpretation, annexin V is an active component because its activity is binding to the cellular target ....

Section 5 of the office action; and:

> ... under the broadest reasonable interpretation, annexin V is an active component of the treatment ....

Section 7 of the office action. However, the claims are now amended to recite the use of "native Annexin V as the active component of the composition or a salt thereof, or a dimer and/or PEG conjugate of the native Annexin V or salt thereof." There clearly is no disclosure in Blankenberg *et al.* of using any of native Annexin V, a PEG conjugate of native Annexin V, a dimer of native Annexin V, or salts thereof, to treat vulnerable plaques. This is for the simple reason that when Annexin V is complexed to additional "effector" and "targeting" portions, such as technetium-99m and porphyrin, respectively, as described in Blankenberg et al, it can clearly no longer be considered to be "native" Annexin V. Nor can Annexin V, when complexed to additional "effector" and "targeting" portions, such as technetium-99m and porphyrin, respectively, as described in Blankenberg *et al.*, be considered to be a dimer of native Annexin V, a PEG conjugate of native Annexin V, or a salt of any of these, as presently recited by the amended claim 4.

It follows, therefore, that Blankenberg et al fails to teach a method of preventing plaque rupture in a subject comprising administering to said subject a pharmaceutical composition comprising an effective amount of native Annexin V as the active component of the composition or a salt thereof, or a dimer and/or PEG conjugate of the native Annexin V or salt thereof. Of

course, in contrast to all of the preceding disclosures, the present claims now recited that the Annexin V is native Annexin V, PEG-ylated Annexin V, or dimerized Annexin V. Thus, applicants submit that claims 4 and 10 are not anticipated by Blankenberg *et al.*, nor could they be rendered obvious. Reconsideration and withdrawal of the rejection are therefore respectfully requested.

IV. Rejection Under 35 U.S.C. §103

Claims 3 and 5 remain rejected as rendered obvious by Blankenberg *et al.* in view of Manzi *et al.* Once again, applicants traverse.

The examiner alleges that Manzi teaches that SLE patients are known to have a greater risk of plaque rupture. However, the examiner admits that Manzi *et al.* is not used to supplement any deficiencies in the teachings of Blankenberg. Thus, the examiner tacitly acknowledges that Manzi says nothing about a potential role for Annexin V in modulating plaque rupture; nor does it suggest that apoptosis should be prevented in order to prevent plaque rupture.

As discussed above, the present claims are now directed to methods that rely on the biological activity of native Annexin V, or a dimer and/or PEG conjugate of the native Annexin V or salt thereof, to treat vulnerable plaques. In contrast, Blankenberg *et al.* only suggests treating vulnerable plaques by using a multi-component complex that includes Annexin V as a binding molecule only when it is ***further complexed*** to a 'targeting portion' molecule like technetium-99m and an 'effector portion' like porphyrin.

This difference goes to the very core of the important technical distinction between the teachings of the present invention and of Blankenberg *et al.* More specifically, the reader of Blankenberg *et al.* would not consider using Annexin V in the treatment of plaque rupture unless

it was also complexed to a 'targeting portion' molecule like technetium-99m and an 'effector portion' like porphyrin, because there is no teaching or suggestion that Annexin V itself provides a biological activity that is capable of preventing the rupture of atherosclerotic plaques on its own. By contrast, the current application provides the first indication and suggestion that an Annexin V molecule provides all of the necessary therapeutic activity on its own to treat plaque rupture.

Thus, the skilled artisan is taught that Blankenberg *et al.* proposes treating plaque rupture using an entirely different composition, having a completely different type of biological activity, than that of the present application. Following from this, the skilled artisan would not find it obvious to attempt a method of preventing plaque rupture by using native Annexin V, or a dimer and/or PEG conjugate of the native Annexin V or salt thereof, as they would have no expectation that this would have any effect on the rupture process. In fact, the overall teaching in Blankenberg is that it is necessary to kill cells in vulnerable atherosclerotic plaques in order to treat those plaques. See Blankenberg *et al.*, paragraph [0032]. The killing of cells is clearly the direct ***opposite*** of preservative consequences that would be expected to follow from the anti-apoptotic effects that are taught by Blankenberg *et al.* to be associated with unlabelled Annexin V. See Blankenberg *et al.*, paragraph [0031].

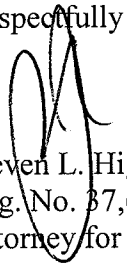
Therefore, the skilled person would understand, from the overall teaching of Blankenberg, that although Annexin V may be suitable as a binding molecule for atherosclerotic plaques, if used alone in a native form, it would be likely to exert a protective effect that is in conflict with the killing effect that is said by Blankenship *et al.* to be useful for treatment of unstable plaques. As a consequence, the skilled person would not be motivated to try, and would be surprised to discover, that the unlabelled, native, Annexin V protein itself could be used to

prevent the rupture of atherosclerotic plaques. Thus, in light of the clear deficiencies with respect to Blankenberg *et al.* in view of the claims as submitted herewith, and the inability of Manzi *et al.* to overcome the shortcomings of Blankenberg *et al.*, as outline above, obviousness has not been established by the evidence of record. Reconsideration and withdrawal of this rejection also is therefore respectfully requested.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



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